Artículo Invitado

Identification of quantitative trait loci in beef cattle*

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ABSTRACT: The objective of this review is to describe the quantitative trait loci (QTL) identified in beef cattle at the U. S. Meat Animal Research Center (MARC), and to describe the process in which they can be incorporated into animal breeding schemes. Four large half-sib families were developed (two families with 500 offspring each, and two families with an average of 227 offspring) to detect QTL for growth, carcass composition and meat quality traits. Scans in these families, using molecular markers obtained from the bovine linkage map, were done. Regions on chromosomes 2, 3, 4, 5, 6, 8, 13, 15, 16, 27, and 29, were detected to harbor genes associated with these traits. Characterization of the variation of the QTL needs to assessed in outbred populations. Animals from the Germplasm Evaluation Project, developed at MARC, are suitable populations in which this can be accomplished. New marker systems able to be used in high-throughput genotyping systems need to be developed to charaterize the QTL variation in outbred populations. A genomic program is being developed at MARC to produce single nucleotide polymorphisms (SNP) from expressed sequence tags (EST). These molecular markers will provide the means to characterize variation of previously identified QTL. The purpose is to use genomic information to either, identify the alleles of a gene that is producing differences in expression of a trait (Functional genomics), or to use this information in selection schemes supported by marker information (Marker-assisted selection).

Key words: Quantitative trait loci, beef cattle, growth, carcass composition, meat quality

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Identificación de características cuantitativas en ganado de carne

RESUMEN: El objetivo de la presente revisión fue describir los loci de caracteres cuantitativos (QTL) que se han identificado en el ganado de carne en el U. S. Meat Animal Research Center (MARC), y describir el proceso por el cual pueden ser incorporados a programas de mejoramiento genético. Se produjeron cuatro familias de medios hermanos (dos familias con progenie de 500 animales, y otras dos con un promedio de 227 animales por familia), para detectar QTL relacionados con las características del crecimiento, de la composición de la canal y de la calidad de la carne. La búsqueda de los QTL se hizo con marcadores moleculares obtenidos del mapa de ligamiento bovino. Se detectaron regiones donde se encuentran los genes asociados con éstos caracteres en los cromosomas 2, 3, 4, 5, 6, 8, 13, 15, 16, 27, y 29. La caracterización de la variación de estos QTL debe hacerse en poblaciones abiertas. Esto se puede lograr utilizando las poblaciones del proyecto de evaluación de germoplasma que se tienen en MARC. Se deben desarrollar sistemas de marcadores moleculares que puedan ser utilizados en sistemas de genotipificación de alta velocidad, para poder caracterizar la variación de los QTL en poblaciones abiertas. Se ha establecido un programa genómico en MARC para desarrollar marcadores conocidos como polimorfismos de nucleótidos sencillos (SNP) a partir de secuencias de DNA expresadas (EST). Estos marcadores moleculares proveerán los medios para caracterizar la variación de los QTL. Se prevé hacer uso de la información genómica para identificar los alelos de un gen que produzcan diferencias en la expresión de un carácter (Genómica funcional), o para usarlos en programas de selección (selección asistida por marcadores).

Palabras clave: Loci de caracteres cuantitativos, ganado de carne, crecimiento, composición de la canal, calidad de la carne

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Introduction

Economically important traits are regulated by the combination of genes and the environment. Alternative forms of a gene are called alleles. Genes are arranged in chromosomes and each species has differing numbers of chromosomes. Genetic markers are tags along the chromosome and can be used to identify the region, or loci, where the genes of interest reside. Genetic markers can be, but do not necessarily need to be, within the gene. This makes them a valuable tool in animal breeding.

The development of polymorphic markers and linkage maps in bovine has made possible the identification of genomic regions where loci influencing economically important traits reside (Kappes *et al*., 1997). Selection of traits of economical importance can be aided by the use of molecular markers. This information could be incorporated in selection schemes to increase the accuracy of predicting the genetic value of an individual (Dentine, 1992). However, in order to use this information, it is imperative to first identify those regions of the genome in which the genes are located. The location of the gene on a chromosome is referred as quantitative trait loci (QTL). It is important to establish the magnitude of the effect that the locus has in the expression of the trait, so selection would be aided by those regions with the most effect on the trait of interest. Once these locus are identified and quantified, they can be used in selection schemes.

Identification of QTL for growth and carcass traits is being done in animals with limited genetic background. Families have been developed and search for QTL has been done, allowing the initial identification of QTL. Establishing segregation of these QTL in outbred populations from several breeds is being pursued.

Characterization of QTL variation in outbred populations will likely be based on a combination of microsatellites and single nucleotide polymorphisms (SNP). Application of functional genomics approaches would significantly enhance characterization of QTL variation by collecting expressed sequence tags (EST) data, and development of markers systems (i.e., SNP haplotypes) suitable for high-throughput genotyping technology.

The procedure used to detect and to use QTL in beef cattle are delineated. The objective of this paper was to review the quantitative trait loci identified in beef cattle at the U. S. Meat Animal Research Center (MARC), and to describe the process in which they can be incorporated into animal breeding schemes.

Linkage maps

The genetic material is organized in chromosomes and a complete set of chromosomes is called a genome. In cattle, 30 chromosomes constitute the genome. Linkage maps, composed of molecular markers, have been developed for this species (Kappes *et al*., 1997; Barendse *et al*., 1997). Molecular markers, also known as genetic markers, have been developed throughout the genome of many domestic species. Examples of genetic markers include restriction fragment length polymorphisms (RFLP), randomly amplified polymorphic DNA (RAPD), minisatellites, microsatellites, and SNP. Each marker has a specific location in the genetic material. Figure 1 shows the location of molecular markers on bovine chromosome 2. A group of markers of a chromosome is called a linkage group and the group of linkage groups is called a linkage map. The total number of molecular markers in different maps is 2850 covering approximately 3000 centimorgans (cM). A centimorgan is a measure of the frequency of recombination rate that occurs in the genome. One centimorgan represents 1 recombination event per 100 meioses and equates to approximately 1 million base pairs in the DNA structure.

The linkage maps have been used to detect the regions where genes that affect production related traits reside. Regions where genes for horn development (Georges *et al*., 1993a), coat color (Charlier *et al*., 1996a; Klungland *et al*., 1995), Weaver disease (Georges *et al*., 1993b) double mus-

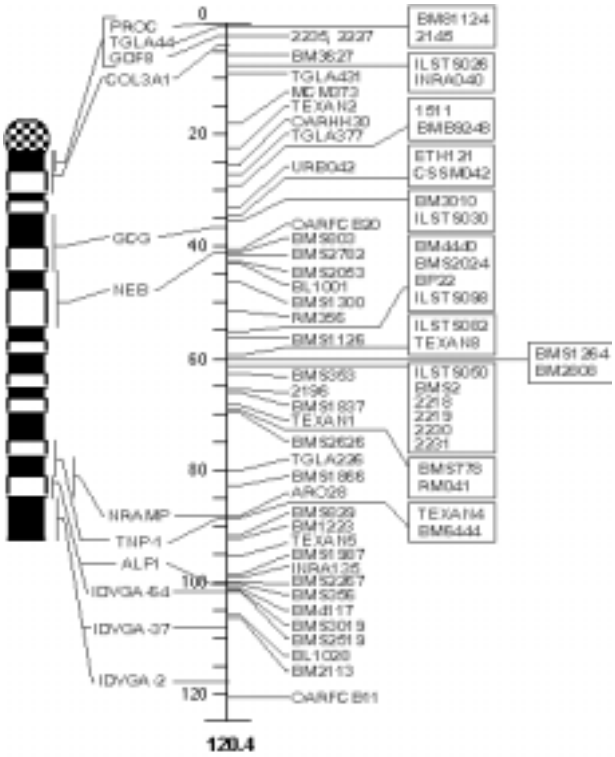

Figure 1. Representation of the linkage group for bovine chromosome 2. The diagram on the right is the linkage group with molecular markers spanning 120.4 centimorgans. The markers on the left side of the linkage group have been physically assigned to specific regions of the chromosome. These markers anchor the linkage group to the chromosome.

cling (Charlier *et al*., 1995) syndactyly (Charlier *et al*., 1996b), milk production (Georges *et al*., 1995), and disease susceptibility (Ashwell *et al*., 1996) reside have been detected in cattle. Several regions harboring genes influencing production traits have been reported. The use of linkage maps have allowed the identification of other regions in which genes for economically important regions in beef cattle have been identified. Following are the results obtained at the U. S. Meat Animal Research Center.

Resource families used to identify QTL

Four resource families were developed for the identification of QTL for growth, carcass composition, and meat quality traits. Two half-sib families were developed from a Brahman X Hereford (BH) or a Brahman X Angus (BA) sires (Keele *et al*., 1999; Stone *et al*., 1999). The BH sire produced offspring during 1994 and 1996, whereas the BA sire produced offspring in 1995 and 1996. Both sires produced approximately 250 offspring per year. Two additional half-sib families were developed from a Belgian Blue X MARC III (BM) or a Piedmontese X Angus (PA) sire (Casas *et al.,* 1998). These families produced 246 and 209 offspring, respectively, in 1995. Families BM and PA were generated primarily to refine the location of myostatin, the gene that produces double-muscling, to identify additional QTL, and to detect interactions between myostatin and other chromosomal regions for carcass composition and meat quality traits.

Quantitative trait loci detected

Detection of QTL is an ongoing effort at MARC. Table 1 shows the QTL of most interest detected to date to characterize variation in outbred populations. Chromosomal location, relative position, according to Kappes *et al.* (1997), trait, and family in which the QTL was detected is shown in this table. Discussion will focus on highly relevant results.

Myostatin, the gene that causes double-muscling in cattle, was studied to establish its effect on growth, carcass composition, and meat quality traits. This gene resides in the centromeric end of chromosome 2 (Smith *et al*., 1997; Casas *et al*., 1998). The allele that causes the condition has a dramatic effect in many traits. We also established epistatic effects of this gene with other chromosomal regions on several traits (Casas *et al*., 2000; Casas *et al*., 2001).

On a distal region from the location of myostatin there is a QTL for carcass traits, identified in the BH family. This QTL cannot be considered the same because of its distance from the centromeric region where myostatin resides. It was impossible to assess if this QTL effect was present in the BM and PA families because the magnitude of myostatin hampered any attempt of analysis.

A QTL for marbling and retail product yield was detected in families BA and BM on chromosome 3. In both families the QTL for the same traits reside in a similar chromosomal region. This suggests it is the same gene, or group of genes, influencing the expression of marbling and retail product yield. In these two families with different genetic background (Belgian Blue and MARC III in one family and Brahman and Angus in the second) the QTL was detected. Alleles inherited from MARC III animals can be from any of the four breeds involved in the composite breed (Hereford, Angus, Red Poll, or Pinzgauer). It is possible that in both families comparisons are made between the Angus allele with the Belgian Blue and Brahman alleles. These results highlight the need to characterize allelic variation of QTL in several breeds and breed crosses to enable effective marker-assisted implementation.

Chromosome 5 has been involved in the expression of traits in beef cattle. In families BH and PA, QTL were detected for rib-eye area, birth weight, marbling, fat depth, retail product yield, USDA yield grade, and the interaction of myostatin, on chromosome 2, with a region on chromosome 5 for a meat tenderness measured as Warner-Bratzler shear force at 14 d postmortem. The QTL reside in a region neighboring the location of the insulin-like growth factor I gene (IGF1). It is impossible to ascertain whether it is a pleiotropic effect of one gene, or different genes closely linked with independent effect on all traits; however, the relative position of each trait tends to support the latter.

Other studies have also identified QTL for growth composition in ortologous regions of chromosome 5. The QTL for carcass composition traits on chromosome 5 are located near IGF1. Moody *et al*. (1996) found an association between IGF1 and growth in Hereford cattle, suggesting the possibility that this, or a closely located gene could be associated with growth. Davis *et al*. (1998) using information from families obtained from a *B. indicus* X *B. taurus* cross, found a QTL for birth weight in the same region. Similar associations have been observed in other species. Collins *et al*. (1993), using markers closely linked to IGF1 detected a QTL associated with growth in mice. Horvat and Medrano (1995), using a population of mice segregating the high growth (hg) locus, mapped the gene to a region near IGF1. It is now known that lack of expression of the suppressor of the cytokine signaling (Socs2) gene is responsible for the high growth phenotype (Horvat and Medrano, 2001). Casas-Carrillo *et al*. (1997) also found a potential QTL associated with growth rate in pigs near IGF1. To date, there are several lines of evidence supporting the existence of a QTL for growth and carcass traits on bovine chromosome 5 in a region closely linked to IGF1. Further studies will be needed to ascertain whether the same gene or genes are responsible for the expression of the traits in different species.

The presence of a QTL for growth and carcass traits was observed on chromosome 6. Davis *et al*. (1998) reported a QTL for birth weight on this chromosome. Furthermore, an estimated effect of 2 kg in one family and 3.8 kg in a second family is very similar to the estimated effect of 3.8 kg from the studies in the BM family. Given that the study of Davis

Table 1. Quantitative trait loci identified in four half-sib resource families.

Chromosome	Rel. position (cM)[a]	Trait	Family[b]	Candidate gene
2	4	Birth weight (kg)	BM, PA	Myostatin
	4	Retail product yield (%)	BM, PA	Myostatin
	4	Rib-eye area (cm^2)	BM, PA	Myostatin
	4	USDA yield grade	BM, PA	Myostatin
	4	Marbling	BM, PA	Myostatin
	4	Fat depth (cm)	BM, PA	Myostatin
	4	KPH	BM, PA	Myostatin
	36	Retail product yield (%)	BH	
	54	Marbling	BH	
	73	Fat depth (cm)	BH	
3	56	Marbling	BA	
	65	Marbling	BM	
	68	Retail product yield (%)	BA	
	70	Retail product yield (%)	BM	
4	30	Hot carcass weight (kg)	BM	
	35	Average daily gain (kg/day)	BM	
	20	Shear force at 3 d postmortem (kg)	BM	
5	53	Rib-eye area (cm^2)	BH	
	57	Birth weight (kg)	BH	
	75	Marbling	BH	
	62	Fat depth (cm)	PA	
	72	Retail product yield (%)	PA	
	68	USDA yield grade	PA	
	70	Shear force at 14 d postmortem (kg)	PA	
6	48	Birth weight (kg)	BM	
	49	Yearling weight (kg)	BM	
	49	Rib-eye area (cm^2)	BM	
	49	Hot carcass weight (kg)	BM	
	55	Fat depth (cm)	BH	
8	9	Marbling	BM	
	24	Fat depth (cm)	BM	
	28	Fat depth (cm)	PA	
13	63	Retail product yield (%)	BH	
15	28	Shear force at 14 d postmortem (kg)	BH	
16	44	Marbling	BA	
	49	Hot carcass weight (kg)	BA	
	62	Kidney, Pelvic & Heart Fat (%)	BA	
	62	USDA yield grade	BA	
27	62	Marbling	BA	
29	54	Shear force at 3 d postmortem (kg)	PA	μ-Calpain
	54	Shear force at 14 d postmortem (kg)	PA	μ-Calpain

[a] cM = Centimorgan.
[b] BM = Belgian Blue X MARC III; PA = Piedmontese X Angus; BH = Brahman X Hereford; BA = Brahman X Angus.

et al (1998) focused on birth weight, no other information is available on the effect of this region on subsequent weights or for carcass traits.

Epistatic interactions between loci have been postulated to exist for QTL (Falconer, 1989), and current technology allows their detection. Microsatellite markers have been successfully used to detect regions on chromosomes 4, 5, and 8 interacting with myostatin for meat tenderness measured as Warner-Bratzler shear force at 3 and 14 d postmortem and with fat depth, respectively. Discussion of interactions will focus on chromosome 8. Evidence suggests that in the BM family there is a direct effect of the QTL on fat depth; whereas, in the PA family there is evidence of an interaction of the same chromosomal region with myostatin, on chromosome 2. Different alleles on the chromosome 8 locus could be involved, given that in one family interacted with myostatin and not in the other. This is the first report of such epistatic interactions in livestock.

Meat tenderness, expressed as Warner-Bratzler shear force, is an economically important trait in the beef industry. A putative QTL was detected on the telomeric end of chromosome 29 in the PA family. Tenderness of meat is determined by the rate and extent of postmortem proteolysis. The calpastatin proteolytic system has a major role and is perhaps responsible for meat tenderization during postmortem storage (Shackelford *et al*., 1995). The calpastatin proteolytic system consists of μ-Calpain, m-Calpain, and Calpastatin. μ-Calpain has been mapped at 54 cM from the most centromeric marker on chromosome 29 (Smith *et al.*, 2000). The location of μ-Calpain and the QTL are the same. This makes μ-Calpain a candidate gene for the QTL detected on this chromosome.

Outbred populations in which characterization of QTL variation is taking place

Detection of QTL is being done in resource families. The currently available results in QTL detection for carcass composition and meat quality traits are based on few large half-sib families. A broader genetic background is needed to establish if the detected QTL segregate. The Germplasm Evaluation project (GPE), from the U. S. Meat Animal Research Center, will provide the outbred populations necessary to characterize variation of detected QTL.

Table 2 shows the sire breeds used in the matings of each cycle of the GPE project that will be used to characterize variation of detected QTL. In each cycle, sires were bred to Angus, Hereford, or MARC III dams. Matings were made to produce straightbreds and reciprocal crosses of Hereford and Angus. Steers produced in the F1 generation were slaughtered and females were kept.

In GPE IV, only animals with Hereford, Angus, and Piedmontese inheritance will be used to characterize variation of detected QTL. F1 females were mated to Hereford, Angus and Piedmontese sires to produce backcrosses. F1 sires were used to generate a population of F2. In this population, there are individuals with 0%, 25%, 50% and 75% of Piedmontese inheritance. This allows us to potentially have 0, 1, or 2 copies of any given allele from each breed at any given loci. Approximately 850 animals were produced and growth traits were measured. From those, approximately 500 animals had carcass composition and meat quality traits measurements (Cundiff *et al*., 1990).

Table 2. Sire breeds used in Germplasm Evaluation Program at MARC.

Cycle IV (1995-2001)	Cycle V (1998-1999)	Cycle VII (1999-2005)
Hereford	Hereford	Hereford
Angus	Angus	Angus
Longhorn	Tuli	Red Angus
Salers	Boran	Limousin
Galloway	Belgian Blue	Charolais
Nellore	Brahman	Simmental
Shorthorn	Piedmontese	Gelbvieh
Piedmontese		
Charolais		
Gelbvieh		
Pinzgauer		

In GPE V, all females produced were used to generate the next generation. Half of the F1 females were mated to Charolais and the other half to F1 sires. The F1 sires were obtained from the mating of Belgian Blue with MARC III. Approximately 1500 offspring were produced. Growth and carcass composition traits were measured in all the animals (Cundiff *et al*., 2000).

GPE VII, is a sample of the current beef industry in the United States. In contrast to other cycles of GPE program, when only young unproven bulls were sampled, about one-half of the sires sampled from each breed were among the top 50 in progeny registrations in their respective herdbooks and about one-half were young unproven bulls (Cundiff *et al*., 2001). All F1 steers are being sent to slaughter and growth, carcass composition, and meat quality traits are being measured on them. F1 females are being kept. Starting in 2001, F1 sires from each cross will be kept and mated to F1 females to produce an F2 population. It is expected that after 2002 there will be 300 offspring per year until 2005. Measurements of growth, carcass composition and meat quality traits will be produced for these animals.

In the future, samples of GPE VIII will also be collected for the same purposes. This cycle will include the following breeds: Hereford, Angus, Bonsmara, Romosinuano, Beefmaster, and Brangus. Some of these breeds are tropically adapted. Characterization of QTL variation in these breeds will be of great importance in tropical and subtropical regions.

These populations were designed to measure breed differences in performance. They represent a valuable resource to determine if QTL already identified are segregating. Identification of these QTL in outbred populations will aid animal breeding programs through marker-assisted selection.

Development of markers to characterize QTL variation

The use of microsatellite markers to validate previously identified QTL in outbred populations is time consuming and difficult to evaluate. Lack of information on QTL phase relative to the microsatellite alleles for each sire and dam poses a difficult problem to overcome when this information does not exist. Marker systems useful for high throughput genotyping are necessary to overcome these problems.

Development of genomic tools has been a priority at MARC since progress in other species, as humans, mice, yeast, etc., has been rapid. Livestock species have lagged behind, limiting the use of functional genomics and QTL analysis in cattle. These last two areas would be enhanced by developing cDNA libraries, collecting expressed sequence tags (EST) data, and generating single nucleotide polymorphism (SNP) markers from EST. Identification of genes residing under QTL would be more efficient if comparative maps between bovine and human were available.

An EST sequencing program has been initiated at MARC. Its objective is to provide bovine-specific information that will facilitate proteomics and functional genomics. To do this, four normalized cDNA libraries were produced. The libraries were made with RNA pooled from multiple tissues to increase efficiency of normalization and maximize the number of independent genes for which sequence data were obtained. Selected tissues included those with highest likelihood to impact animal health, growth, reproduction, carcass composition and meat quality. Table 3 shows the tissues included in each library. These libraries generated between 20,000 to 24,000 sequences each for a total of 90,665 independent sequences. The sequences were deposited in GenBank. Sequence comparison and assembly was done in combination with other bovine EST GenBank dbEST sequences to construct a cattle gene index. The bovine EST sequences present in GenBank at the time of the analysis made 16 740 assemblies that are listed and annotated on The Institute for Genomic Research web site (www.tigr.org/tdb/tgi.shtml). Results of this effort have been made public (Smith *et al*., 2001).

The increase of bovine EST provide the resources needed to map SNP. Single nucleotide polymorphism information will provide the data needed to integrate EST into the bovine linkage map (Kappes *et al*., 1997). The goal of the EST-SNP is to place at least 1000 EST on the bovine linkage map by developing a single SNP from each EST. This will provide the basis for future development of SNP within the same EST, generating SNP haplotypes at selected intervals over the entire genome to conduct genomic scans or to characterize variation of previously identified QTL in outbred populations.

The use of SNP as markers in association studies has been discussed (Cargill *et al*., 1999). Single nucleotide polymorphisms as markers in livestock have the advantage over microsatellites in that they will usually provide a direct link through sequence orthology to more extensive maps and related information in other organisms. To date we have used the human genomic sequences to integrate more than 300 bovine EST into existing linkage maps using SNP as markers. With bovine EST and the human draft sequence as resources, it should be possible to target any genomic interval or candidate gene for SNP marker development. Development of markers based on SNP haplotypes, to provide genome-wide coverage, will require additional EST mapping and sequencing. The usefulness of such group of markers will depend on high throughput genotyping platforms.

Development of markers suitable for high throughput genotyping will provide the means to characterize variation of previously identified QTL. The objective of the EST-SNP project at MARC is to generate the marker systems needed to evaluate QTL in outbred populations. This will let the incorporation of marker information in animal breeding schemes through marker-assisted selection. It will also permit the incorporation of functional genomics to eluci-

Table 3. Tissues included in each MARC bovine EST library.

MARC 1BOV	MARC 2BOV	MARC 3BOV	MARC 4BOV
Mesenteric lymph node	Testis	Bone marrow	Whole embryos
Hilar lymph node	Thymus	Alveolar macrophage	
Pos-pubertal ovary	Semitendinosus muscle	Pre-pubertal ovary	
Kidney-associated fat	Longissimus muscle	Fetal semitendinosus muscle	
Hypothalamus	Pancreas	Fetal longissimus muscle	
Pituitary	Adrenal gland		
Subcutaneous fat	Endometrium		

date the function of candidate genes in the physiological pathways associated with traits of interest.

Implications

The use of molecular markers offers a great potential to improve efficiency of animal breeding. Development of cost effective techniques and their integration into production systems is the challenge. Techniques to isolate and evaluate DNA have revolutionized our understanding of, and ability to regulate, the biological processes that are involved in the development of economically important traits.

Develop new technology to increase the efficiency of livestock production and benefit consumers is the challenge. With this objective, a program has been developed at MARC to identify the chromosomal regions where genes influencing growth, carcass composition, and meat quality traits reside. Characterizing the variation of these regions using outbred populations currently being developed on-center will be done. Novel marker systems for high throughput genotyping need to be developed to allow this characterization. The purpose is to use genomic information in either, functional genomics studies or in marker-assisted selection to improve the efficiency in animal breeding schemes.

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